REMARKS

After entry of this amendment, the claims pending are claims 1, 2, and 4-15. Claims 16-20 are cancelled. Claim 3 was previously cancelled. Any subject matter canceled from the claims by amendment is reserved for refiling in a continuation application filed during the pendency of this application. Applicants further affirm the correctness of the inventive entity in view of the cancellation of claims.

Claim 15 is amended to insert the words "*in vivo*" into the claim. Support for this amendment is found in the specification and particularly on pages 88-90. No new matter is introduced by this amendment.

A. Rejections Under 35 USC §112, first paragraph

Claims 15-20 are rejected under 35 USC §112, first paragraph, for lack of enablement. The examiner states that the specification does not reasonably provide enablement for the *in vivo*/whole animal application of antisense oligonucleotides targeted to SEQ ID NO: 3.

Without addressing the substance of this rejection and in an earnest attempt to advance prosecution, Applicants have cancelled claims 16-20 and reserve the right to file same in a continuation application filed during the pendency of this application. Claim 15 has been amended to insert the word "*in vivo*" after "tissues" on line 3. In view of these amendments, Applicants respectfully request reconsideration and withdrawal of this rejection.

B. Rejections Under 35 USC §103(a)

Claims 1-14 are rejected under 35 USC §103(a) as being unpatentable over the following combination of six documents:

(1) A. E. Sluder *et al*, **1997** *Devel. Biol.*,184:303-319 ("Sluder")

(2) H. Nishigori *et al*, **2001** *Proc. Natl. Acad. Sci., USA, 98*(2):575-580 ("Nishigori")

(3) US Patent No. 5,801,154 ("Baracchini")

(4) US Patent No. 5,998,148 ("Bennett")

(5) H. M. Weintraub, **Jan. 1990** *Scient. Amer.*, pp.40- 46; and

(6) Applicants' admission that GenBank Accession No. L76571 is the published RNA sequence of human short heterodimer partner-1 at specification page 86.

The examiner states that one skilled in the art would have been motivated to make antisense oligos targeted to SHP-1, since SHP-1 has been linked to obesity (Nishigori) and since art has shown the use of antisense in determination of function of a SHP-1 (Sluder). Bennett and Baracchini are cited to indicate that antisense functions as a tool for gene study and that one may modify the oligos and deliver same to cells and for providing general rules for antisense design. Weintraub is cited for teaching that antisense oligos will be used in treatment of diseases and as research tools. Targeting of SHP-1 is asserted to be an obvious choice since it was a known and published sequence (GenBank).

Applicants respectfully request reconsideration and withdrawal of this rejection in view of the above amendments to the claims and the following remarks.

The combination of the above-cited six references fails to make a prima facie case of obviousness against the pending claims of this application.

A. Sluder's nhr-2 gene is not an equivalent to human short heterodimer protein-1 of the present invention and thus suggests nothing related to the instant claims, whether taken alone or in combination with the additional 5 references.

The short heterodimer partner-1 (SHP-1), as described in the specification is a nuclear receptor subfamily 0 group B member. Human SHP-1 is described as ***an unusual member*** of the orphan receptor family (see specification page 2, lines 1-5), and is believed to be involved with obesity. A sequence for its RNA is published by GenBank, as also referenced in the specification.

Nhr-2 is not an "equivalent" of SHP-1. In contrast, Sluder refers to this nematode gene, nhr-2, as a member of the nuclear hormone receptor superfamily that "defines a *new subclass* of the superfamily". Nhr-2 is involved with early embryonic development.

The nuclear hormone receptor *superfamily* is an enormous collection of receptors which share some structural and functional similarities. However, variations among the genes falling within that umbrella term are considerable, resulting in families, further divided into subfamilies, and further divided into groups, classes and subclasses. Sluder mentions a number of nuclear receptor superfamily subclasses, e.g., glucocorticoid receptor subclass, estrogen subclass, thyroid hormone class and retinoid receptor class. Sluder teaches that the injection of an unspecified antisense RNA into the syncytial region of the hermaphrodite gonad disrupts the function of nhr-2 in embryonic development.

Applicants are aware of no art or facts that support the examiner's contention that nhr-2 is an equivalent of SHP-1. In fact, Sluder itself states:

> "Second, outside the DNA binding domain, nhr-2 exhibits no significant similarity to known members of the NHR superfamily." (page 315, col. 2)

Additionally, Applicants compared the Sluder sequence for nhr-2 (GenBank Accession No. NM_021969) with the GenBank Accession No. L76571 for human SHP-1 (SEQ ID NO: 3) and found no significant sequence homology at the gene or protein levels.

Applicants therefore contend that the examiner has inappropriately cited Sluder as a reference relevant to this application. Applicants respectfully request that if the examiner has evidence unknown to Applicants to conclude that these two genes are related, e.g., a BLAST search, etc., that such evidence be shown to Applicants. As it now stands, Applicants cannot find any basis upon which to conclude that nhr-2 has any meaningful equivalence to SHP-1 (SEQ ID NO: 3).

In view of the lack of equivalence between these genes, Applicants respectfully submit that the examiner's characterization that Sluder teaches the use of an antisense sequence that disrupts expression of a gene equivalent to SHP-1, is incorrect. Sluder's teachings with respect to an unrelated gene to SHP-1 are simply not capable of suggesting anything with respect to the claims of the present invention.

Sluder contains no disclosure that suggests or refers to the SHP-1 gene or its encoded protein. Without any disclosure of SHP-1, Sluder cannot provide any suggestion that permits one to identify or suggest specific SHP-1 sequences as target sequences for binding by an antisense sequence. Sluder does not teach or suggest any sequence for antisense compounds that bind to SHP-1, as required by claim 1. Nor does Sluder suggest any methods for inhibiting SHP-1. Sluder does not teach or suggest a therapeutic utility of antisense compounds that bind SHP-1.

B. Nishigori and the GenBank reference in the specification are the only references relating to SHP-1. Neither reference adds anything relevant to Sluder

Nishigori refers to SHP as modulating the transcription activity of maturity-onset diabetes of the young (MODY) protein. Mutations resulting in the loss of expression of this gene were located in subjects with MODY. Nishigori concluded that genetic variation in the SHP gene contributed to increased body weight. Nishigori says nothing about antisense sequences and merely suggests in the conclusion of the paper that the activity of SHP could be regulated by "*yet-unidentified* ligands". See, page 479, col. 2.

Nishigori thus adds nothing to the unrelated Sluder disclosure. Nishigori does not itself teach or suggest antisense sequences to SHP-1. Nishigori does not suggest antisense sequences to any portion of SHP-1. Nishigori's conclusion is frankly nothing more than a "wish list" for someone to identify some "yet-unidentified ligand", which then may be tested for the ability to impact the function of the SHP-1 gene.

Applicants' reference to the GenBank Accession number of an SHP-1 (SEQ ID NO: 3) is no more than an acknowledgement that SHP-1 was a known nucleic acid/amino acid molecule prior to the filing date. This fact was never in contention. Further, the existence of SHP-1 sequences does not suggest antisense sequences to SHP-1 or to any portion of SHP-1. The GenBank sequence disclosure does not suggest any method of using antisense sequences to SHP-1, when combined with any of the cited references.

Neither Nishigori nor GenBank add any necessary suggestions to make their combination with Sluder, nor with any of the following three references, meaningful.

C. ***The remaining three cited documents teach nothing regarding SHP-1 or antisense sequences capable of inhibiting SHP-1 activity.***

Weintraub is nothing more or less than a review article relating to the field of antisense RNA or DNA, that was 11 years old at the time this application was filed. It adds nothing of relevance to this art combination, since Weintraub does not teach or suggest antisense sequences to SHP-1. Weintraub does not suggest antisense sequences to any portion of SHP-1. Weintraub does not teach or suggest any uses of antisense sequences with regard to inhibiting SHP-1 expression, as is required by the present claims.

Bennett refers to antisense compounds that modulute a *completely unrelated protein* to SHP-1, namely microtubule-associated protein 4 (MAP4). Baracchini refers to antisense compounds that modulute another *completely unrelated protein* to SHP-1, namely multidrug resistance-associated protein (MRP). Neither Bennett nor Baracchini contains any disclosure that suggests or refers to the protein SHP-1. Without any disclosure of SHP-1, neither Bennett nor Baracchini can provide any suggestion that permits one to identify or suggest any SHP-1 sequences as target sequences for binding by an antisense sequence. Neither Bennett nor Baracchini teaches or suggests any sequence for antisense compounds that bind to SHP-1, as required by claim 1. Nor does Bennett or Baracchini suggest any methods for using the sequences of claim 1. Neither Bennett nor Baracchini teaches or suggests a therapeutic utility of antisense compounds that bind SHP-1. These two references are discussed merely for their essentially duplicate, generic teachings related to antisense compounds.

Applicant agrees with the examiner that US Patent 6,121,047 refers to a completely different protein from short heterodimer partner-1, which shares merely the acronym SHP and thus will not be further discussed.

D. ***The combination of these six references does not make a prima facie case of obviousness with regard to the pending claims.***

Applicants respectfully submit that an obviousness rejection based on a combination of documents which disclose

(1) the sequence of SHP-1 (GenBank admission),

(2) a wish for "yet-unidentified" sequences to inhibit its expression (i.e., Nishigori), and

(3) documents cited merely to disclose generic antisense teachings or to disclose antisense sequences to unrelated proteins (i.e., Weintraub, Bennett/Baracchini, and Sluder)

is defective for several reasons.

First, taking each reference as a whole, this combination does not provide any *suggestion* of the antisense sequences of claim 1. An obviousness rejection cannot be made by combining documents to make the bald suggestion that it is "obvious to try" to make antisense compounds to target SHP-1 simply because others have made antisense compounds to other non-related proteins. The US patent law has long held that the "obvious to try" standard is not the appropriate standard for a determination of patentability.

Second, in the above rejection, the examiner has selected only isolated teachings from each reference, and ignored other teachings of those same references.

For example, only the generic teachings of Bennett/Baracchini with respect to antisense compounds are selected, without regard to the fact that Bennett/Baracchini are directed to completely different (both structurally and functionally) proteins. The same can be said for Sluder. The rejection combines these selected components with Nishigori's admitted desire for ***unspecified*** ligands to SHP-1, and Weintraub's generic teachings regarding antisense technology to purportedly make a *prima facie* case of obviousness of the claimed invention.

It is wholly inconsistent with established patent law that only that portion of each cited document that supports the examiner's position is relied upon in the rejection, while the remaining teachings of the combined cited documents are ignored as if irrelevant. This type of construction of an obviousness rejection disregards the standard patent law that references must be taken as a whole, not in pieces.[1]

Third, the only motivation to perform such a combination of components is derived from Applicants' disclosure. The combination of these prior art references to reject the pending claims of the present application is based simply on a prior reading of Applicants' invention. The examiner may not use Applicants' disclosure as a blueprint for piecing together prior art to defeat patentability in an improper manner. One of skill in the art would not have made this combination of elements, i.e., a description of protein SHP-1 and combined with a disclosure relating to anti-sense

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1 *In re Oetiker*, 977 F2d 1443, 24 USPQ 2d 1443, 1446 (Fed. Cir. 1992) "There must be some reason, suggestion, or motivation found in the prior art whereby a person of ordinary skill in the field of the invention would make the combination. That knowledge cannot come from the applicant's invention itself."

compounds that hybridize to ***other*** proteins, without the impermissible application of hindsight.[2] The examiner's reliance on hindsight is clearly improper. The mere fact that the prior art may be modified in the manner suggested by the examiner does not make the modification obvious, unless the prior art *suggested* the desirability of the modification. As discussed above, the prior art references in combination and taken as a whole do not suggest the claimed invention.

Applicants are not claiming "how to make" generic antisense compounds. Applicants' claims are directed to novel antisense compounds that are neither taught nor suggested by these references in combination. The knowledge of antisense technology taken with a sequence of SHP-1, and an author's hope that yet-unidentified antagonists may prove useful in treating a disease to which this protein is believed to be implicated does not provide the required motivation for selection of particular SHP-1 sequences. Nor does such a combination provide any prediction of success with respect ***to SHP-1*** as the target. The cited references, taken together as a whole, do not make obvious the presently claimed invention.

The combination of these references does not provide any *expectation of success* that if one did target the ***specifically claimed*** SHP-1 SEQ ID NO: 3 sequence of the present claims, that one would obtain antisense sequences with the desired inhibitory result. The only source of the required motivation to make and use

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[2] See, e.g., *In re Dembiczak*, 50 USPQ2d 1614, 1616-1617 (Fed. Cir. 1999): "Our case law makes clear that the best defense against the subtle but powerful attraction of a hindsight-based obviousness analysis is rigorous application of the requirement for a showing of the teaching or motivation to combine prior art references. ... Combining prior art references without evidence of such a suggestion, teaching, or motivation simply takes the inventor's disclosure as a blueprint for piecing together the prior art to defeat patentability - the essence of hindsight. ..."

antisense compounds directed to specific sequences of SHP-1 is provided by the Applicants' own specification. The only teachings that supply the necessary motivation and expectation of success that such a composition would be useful are provided by the instant specification. Obtaining the motivation for combination of the prior art cannot properly be provided by Applicants' own disclosure.

Applicants maintain that the combination of the cited prior art, when the teachings are taken *as a whole*, fails to supply both the motivation and a reasonable expectation of success required to set forth obviousness of the pending claims.

In view of the above amendments and these remarks, Applicants' respectfully request that the examiner withdraw the outstanding rejections and permit the above pending claims to pass to issue in due course.

The Director is hereby authorized to charge any additional fees required with the filing of this paper or credit any overpayment in any fees to our deposit account number 08-3040.

Respectfully submitted,

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